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Absence of ECG Task Force Criteria does not rule out structural changes in genotype positive ARVC patients

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ABSTRACT

Aims: In Arrhythmogenic Right Ventricular Cardiomyopathy (ARVC), electrophysiological pathology has been claimed to precede morphological and functional pathology. Accordingly, an ECG without ARVC markers should be rare in ARVC patients with pathology identified by cardiac imaging. We quantified the prevalence of ARVC patients with evidence of structural disease, yet without ECG Task Force Criteria (TFC).

Methods and results: We included 182 probands and family members with ARVC-associated mutations (40 ± 17 years, 50% women, 73% PKP2 mutations) from the Nordic ARVC Registry in a cross-sectional analysis. For echocardiography and cardiac MR (CMR), we differentiated between "abnormalities" and TFC. "Abnormalities" were defined as RV functional or structural measures outside TFC reference values, without combinations required to fulfill TFC. ECG TFC were used as defined, as these are not composite parameters. We found that only 4% of patients with ARVC fulfilled echocardiographic TFC without any ECG TFC. However, importantly, 38% of patients had imaging abnormalities without any ECG TFC. These results were supported by CMR data from a subset of 51 patients: 16% fulfilled CMR TFC without fulfilling ECG TFC, while 24% had CMR abnormalities without any ECG TFC. In a multivariate analysis, echocardiographic TFC were associated with arrhythmic events.

Conclusion: More than one third of ARVC genotype positive patients had subtle imaging abnormalities without fulfilling ECG TFC. Although most patients will have both imaging and ECG abnormalities, structural abnormalities in ARVC genotype positive patients cannot be ruled out by the absence of ECG TFC.

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1. Introduction

Arrhythmogenic Right Ventricular Cardiomyopathy (ARVC[2]) is an inherited disease resulting in electrophysiological abnormalities and potentially fatal arrhythmias, as well as contractile dysfunction that most commonly involves the right ventricle (RV), but can also affect the left ventricle or both [1]. The diagnosis of ARVC is complex and summarized in the 2010 modified Task Force Criteria (TFC) [2]. Genetic testing of ARVC families has resulted in identification of ARVC-related mutations even in patients without or with only mild disease phenotype, and enabled studies on early signs of disease [3]. Early detection of ARVC is crucial, as ventricular arrhythmias may be the first disease manifestation [4–6]. Previous studies have proposed a "concealed phase" of ARVC with increased risk of ventricular arrhythmias before the occurrence of structural changes [7,8]. However, recent studies have identified simultaneous occurrence of electrocardiographic and echocardiographic changes in early disease [9]. We aimed to quantify the proportion of ARVC patients that have structural changes identified by common imaging methods, but without electrophysiological changes identified by ECG.

2. Methods

2.1. Study population and data inclusion

Data for this cross-sectional study were extracted from the Nordic ARVC Registry. At data extraction, the registry included 631 patients with ARVC and their first-degree relatives enrolled from eight centers in Norway, Denmark, and Sweden. The registry comprises clinical characteristics, mutation status, and the results of diagnostic assessments by ECG, echocardiography, and CMR as previously reported [10]. These data are the results of evaluations performed by experts on ARVC at each participating center. Data were extracted on December 14th 2016. The study was approved by the Regional Committees for Medical Research Ethics, and all patients in the registry signed an informed consent form, except for Denmark where approval by an ethics committee is not needed for observational registries. The inclusion and use of data complied with the Declaration of Helsinki.

All probands and relatives in the registry with a mutation considered pathogenic for ARVC (major TFC criterion) were included. Based on this inclusion criteria, by definition all patients fulfilled criteria for the diagnosis of possible, borderline or definite ARVC according to 2010 TFC [2]. The diagnosis of all patients in the registry is based on all TFC, which comprises criteria based on cardiac morphological and functional measurements from imaging, data from ECG and signal averaging ECG, history of arrhythmias, family history and presence of mutations associated with ARVC. A *definite* diagnosis is fulfilled by two major, or one major and two minor criteria, or four minor criteria from different categories; a *borderline* diagnosis is fulfilled by one major and one minor, or three minor criteria from different categories; and a *possible* diagnosis is fulfilled by one major or two minor criteria from different categories. We used the first available data in the registry for each patient, but for inclusion, ECG and echocardiographic data had to be available from the same calendar year. In a subset of patients, CMR data were also available from the same calendar year.

2.2. Individual abnormalities vs. Task Force Criteria

All analyses were based on reference values as provided in the 2010 TFC [2]. To increase the sensitivity for structural changes, we also defined the term "individual abnormality" for findings associated with ARVC that are outside echocardiography and CMR TFC reference values, but not necessarily fulfill the combination of akinesia or dyskinesia together with right ventricular outflow tract (RVOT) and RV fractional area change (RV FAC) cutoffs according to the 2010 TFC [2]. We also combined CMR and echocardiographic data in an analysis of "individual imaging abnormalities" and "imaging TFC", respectively. A similar separation of TFC and individual abnormalities was not performed for ECG, as ECG TFC are not composite criteria, as opposed to imaging TFC. We therefore used ECG TFC throughout the comparisons.

2.3. ECG data

We recorded the presence of T-wave inversion (TWI) in precordial leads, Epsilon wave, and the terminal activation duration of the QRS complex. Presence of RBBB was also noted, but was only considered ARVC-associated when combined with TWI in V1-V4. We defined "ECG TFC" as either minor or major ECG TFC [2].

2.4. Echocardiographic data

We collected 2D echocardiographic data according to reference values from TFC [2]: PLAX RVOT ≥32 mm (major) or ≥ 29 mm (minor); PSAX RVOT ≥36 mm (major) or ≥ 32 mm (minor); RV FAC ≤ 33% (major) or ≤ 40% (minor). The presence of RV akinesia, dyskinesia or aneurysm was noted. We defined "echocardiographic TFC" as measurements fulfilling minor or major TFC, i.e. RVOT or RV FAC measures outside TFC reference values combined with akinesia, dyskinesia or aneurysm identified from qualitative assessments. "Individual echocardiographic abnormalities" were defined as any measurements outside of the TFC reference values, e.g.: PLAX RVOT ≥29 was considered an "abnormality", but not a TFC unless RV akinesia, dyskinesia or aneurysm were present.

2.5. Cardiac MR data

We registered CMR data according to reference values from TFC [2]. CMR TFC reference values for major criteria are: Ratio of RV end-diastolic volume to body surface area (BSA) ≥ 110 mL/m^2 for males or ≥ 100 mL/m^2 for females, and RV FAC ≤ 40%. CMR TFC reference values for minor criteria are: Ratio of RV end-diastolic volume to BSA ≥100 mL/m^2 for males or ≥ 90 mL/m^2 for females, and RV FAC ≤ 45%. We defined "CMR TFC" as measurements fulfilling minor or major TFC, i.e. RV end-diastolic volume or RV FAC measures outside TFC reference values combined with akinesia, dyskinesia or dyssynchronous RV contraction identified by qualitative assessments. "Individual CMR abnormalities" were defined as any measurements outside of the TFC reference values, but not a TFC unless akinesia, dyskinesia or dyssynchronous RV contraction were present.

2.6. Genetic analyses

Peripheral blood was used for isolation of genomic DNA, and genetic analysis was performed as previously described [11]. The analyses were performed at each participating center. Tests were made for mutations in the following genes: plakophilin-2 (*PKP2*), plakoglobin (*JUP*), desmoplakin (*DSP*), desmoglein-2 (*DSG2*), desmocollin-2 (*DSC2*), transmembrane protein 43 (*TMEM43*), ryanodine receptor type 2 (*RyR2*). We used the definition of pathogenic mutations provided in the 2010 TFC [2]. Only individuals carrying mutations considered pathogenic or likely pathogenic were included. The genetic analyses were performed at the discretion of each participating center using the techniques available at the time of evaluation.

2.7. Arrhythmic events

Patients with arrhythmic events were defined as those who originally were evaluated for ARVC due to ventricular arrhythmias and

[2] ARVC Arrhythmogenic Right Ventricular Cardiomyopathy; CMR Cardiac Magnetic Resonance; FAC Fractional Area Change; PLAX Parasternal Long Axis; PSAX Parasternal Short Axis; RV Right Ventricle; RVOT Right Ventricular Outflow Tract; TFC Task Force Criteria

Table 1
Clinical characteristics and prevalence of ARVC-associated abnormalities in 182 patients.

		All N = 182		Probands N = 65		Family members N = 117		P
		N	%	N	%	N	%	
Women		91	50	25	39	66	56	0.03
Probands		65	36					
Age (years±SD)		40 ± 17		43 ± 15		39 ± 17		
Definite ARVC diagnosis		95	52	60	92	35	30	< 0.0001
Borderline ARVC diagnosis		32	18	3	5	29	25	< 0.001
Possible ARVC diagnosis		55	30	2	3	53	45	< 0.0001
Mutations (All major TFC)								
Plakophilin-2, *PKP2*		133	73	49	75	84	72	0.66
Desmoglein-2, *DSG2*		23	13	6	9	17	15	0.24
Desmoplakin, *DSP*		12	7	6	9	6	5	0.29
Transmembrane protein 43, *TMEM43*		8	4	2	3	6	5	0.52
Desmocollin-2, *DSC2*		4	2	1	2	3	3	0.68
Plakoglobin, *JUP*		1	1	0	0	1	1	0.42
Ryanodine receptor type 2, *RYR2*		1	1	1	2	0	0	0.13
ECG								
TWI in V1 and V2 *(Minor TFC)*		67	37	44	68	23	20	< 0.0001
TWI in V1-V3 or more in absence of complete RBBB *(Major TFC)*		53	29	36	55	17	15	< 0.0001
TWI in V1-V4 and RBBB *(Minor TFC)*		2	1	1	2	1	1	0.57
TWI in V4, V5 or V6 *(Minor TFC)*		35	19	27	42	8	7	< 0.0001
Epsilon wave *(Major TFC)*		6	3	5	8	1	1	0.01
Terminal activation duration of QRS >55 ms *(Minor TFC)*		10	6	8	12	2	2	0.005
Any of the ECG abnormalities above		**74**	**41**	**50**	**77**	**24**	**21**	< **0.0001**
Any TFC for ECG		**74**	**41**	**50**	**77**	**24**	**21**	< **0.0001**
Echocardiography								
Regional RV akinesia or dyskinesia		58	32	41	63	17	15	< 0.0001
RV aneurysm		36	20	26	40	10	9	< 0.0001
PLAX RVOT	≥32 mm *(Major TFC if regional RV akinesia, dyskinesia, or aneurysm)*	87	48	42	65	45	39	< 0.001
	≥29 to <32 mm *(Minor TFC if regional RV akinesia or dyskinesia)*	27	15	6	9	21	18	0.10
PSAX RVOT	≥36 mm *(Major TFC if regional RV akinesia, dyskinesia, or aneurysm)*	46	25	26	40	20	17	< 0.001
	≥32 to <36 mm *(Minor TFC if regional RV akinesia or dyskinesia)*	33	18	8	12	25	21	0.13
RV FAC	≤33% *(Major TFC if regional RV akinesia, dyskinesia, or aneurysm)*	24	13	8	12	8	7	0.26
	>33% to ≤40% *(Minor TFC if regional RV akinesia or dyskinesia)*	31	17	13	20	19	16	0.50
Any of the echocardiographic abnormalities above		**134**	**74**	**54**	**83**	**80**	**68**	**0.03**
Any Task Force Criteria for echocardiography		**53**	**29**	**39**	**60**	**14**	**12**	< **0.0001**
Arrhythmias								
Contact due to arrhythmic events		55	30	47	72	8	7	< 0.0001
Arrhythmias major TFC (VT with LBBB morphology and superior axis)		32	18	28	43	4	3	< 0.0001
Arrhythmias minor TFC (VT of RVOT config. or unknown axis or > 500 VES/24 h)		42	23	29	45	13	11	< 0.0001

Data are presented as number of cases and percentage of population unless otherwise stated. BSA Body surface area, CMR Cardiac magnetic resonance, FAC Fractional area change, LBBB Left bundle branch block, PLAX Parasternal long axis, PSAX Parasternal short taxis, RBBB Right bundle branch block, RV Right ventricle, RVOT Right ventricular outflow tract, TFC Task force criteria, TWI T wave inversion, VT Ventricular tachycardia. *P* value for probands vs relatives. Bold indicates the main take-home-data that are directly refered to in the text.

those who had documented major arrhythmia TFC (non-sustained or sustained ventricular tachycardia of left bundle-branch morphology with superior axis), and minor arrhythmia TFC (non-sustained or sustained ventricular tachycardia of RV outflow tract configuration, left bundle-branch block morphology with inferior axis or of unknown axis, or ≥ 500 ventricular extra systoles per 24 h).

2.8. Statistical analysis

Nominal and categorical data were presented as number of cases and percentage of a population, and were analyzed by Chi-square, Fischer's exact test, or N-1 Chi-square. Continuous variables were presented as mean ± standard deviation and were analyzed by *t*-tests. Bonferroni corrections were used for multiple comparisons. Logistic regression analyses were performed with arrhythmic events as dependent variable. *P*-values <.05 were considered statistically significant.

3. Results

3.1. Study population

We included 182 probands and family members from 88 families with a mutation considered pathogenic for ARVC (Table 1). The mean age at first available examination was 40 ± 17 years, 50% were women, and 65 patients (36%) were probands (Table 1). Fifty-five patients (30%) fulfilled criteria for possible, 32 (18%) borderline, and 95 (52%) fulfilled criteria for definite ARVC diagnosis. The most commonly affected gene was *PKP2* (133 patients, 73%), followed by *DSG2* (23 patients, 13%), while mutations in other genes were comparably rare (Table 1). CMR data were available from 51 patients (28%) in whom the background data were similar to the total population (Supplementary Tables 1 and 2).

3.2. Prevalence of patients with structural changes without ECG changes

We identified the proportion of patients that had structural changes as identified by cardiac echocardiography, but not electrophysiological changes identified by ECG (Fig. 1). We found that only 4% of patients fulfilled echocardiographic TFC, and still had no TFC in the ECG (Fig. 1, upper panel). To increase the sensitivity for structural abnormalities, we also performed a similar analysis with "individual echocardiographic abnormalities" using the parameter values for RVOT diameter and RVFAC used in the TFC, but without demanding the combination with RV akinesia, dyskinesia or aneurysm required to fulfill TFC. By this analysis, 38% of patients had echocardiographic abnormalities, yet without TFC in the ECG (Fig. 1, upper panel).

We validated the echocardiographic findings by repeating the analyses with data from CMR. We found that 16% of patients fulfilled CMR

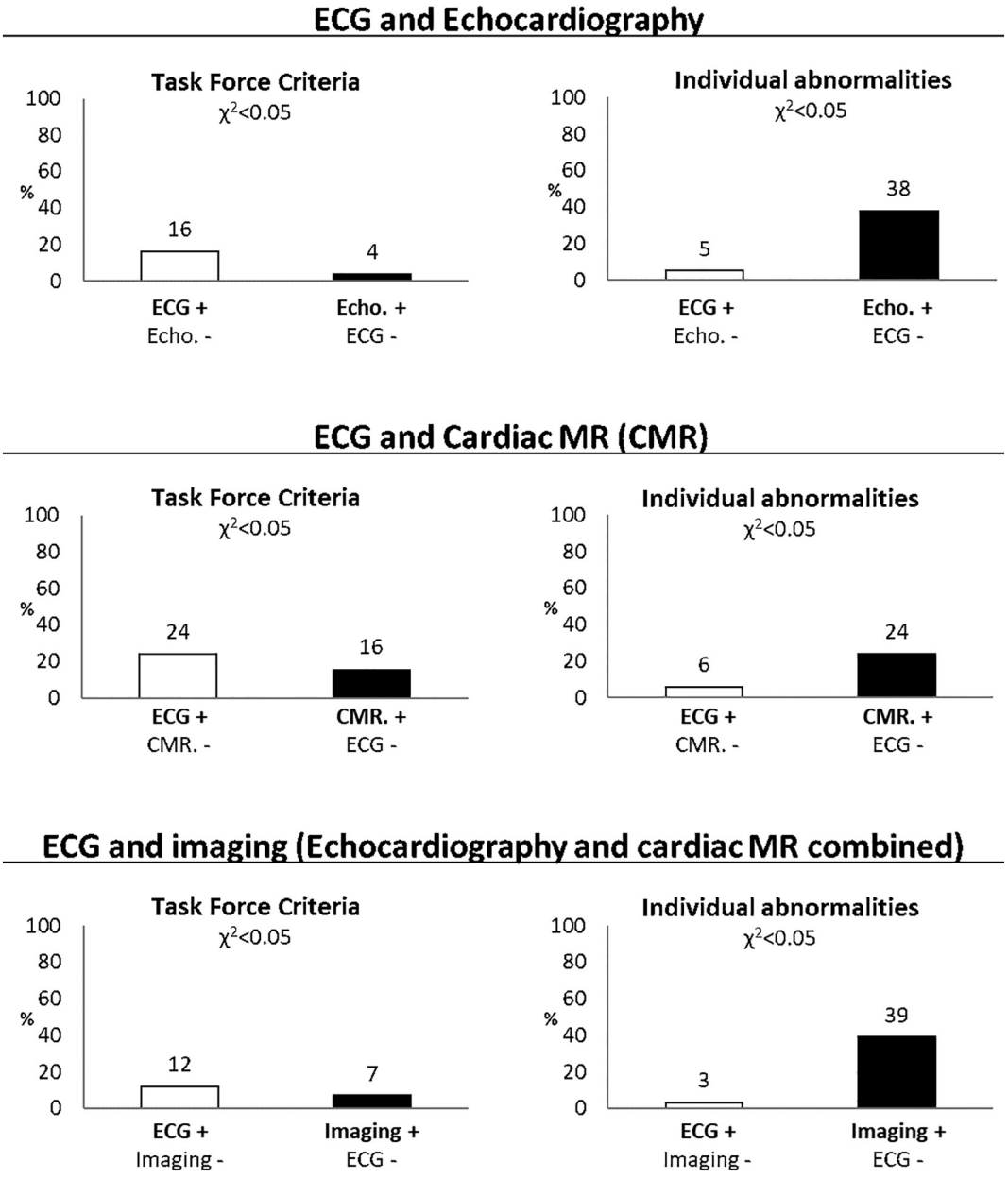

Fig. 1. *Upper left panel:* Percentage of patients with ECG TFC without echocardiographic TFC (ECG +/echo. -), and with echocardiographic TFC without ECG TFC (Echo +, ECG -), respectively. *Upper right panel:* Corresponding data with the use of echocardiographic abnormalities as opposed to TFC. *Middle panels:* Corresponding data from CMR, with use of CMR TFC in the left panel, and CMR abnormalities in the right panel. *Lower panels:* Corresponding data from echocardiographic and CMR combined as "imaging".

TFC without TFC in the ECG (Fig. 1, middle panel). When we increased the sensitivity by using individual abnormalities, 24% of patients had abnormalities identified by CMR without fulfilling TFC in the ECG (Fig. 1, middle panel).

In a third analysis, we combined data from echocardiography and CMR. We found that 7% of patients had structural changes as defined by the TFC for echocardiography and/or CMR without TFC in the ECG (Fig. 1, lower panel). In the more sensitive analysis using individual abnormalities, 39% of patients had structural abnormalities identified by echocardiography and/or CMR without electrophysiological changes as defined by TFC for ECG (Fig. 1, lower panel).

3.3. Subgroup analysis

We performed a separate analysis of family members (Table 1). We found that 4% of family members fulfilled echocardiographic TFC without TFC in the ECG. When individual abnormalities were considered, 51% had echocardiographic abnormalities without fulfilling TFC in the ECG.

Results for diagnostic subgroups (possible, borderline, definite) are shown in Supplementary Table 3.

3.4. Patients with no TFC-defined ECG changes

We further analyzed the subgroup of patients that did not fulfill any ECG TFC ($N = 108$, 59% of all patients, Table 2). Among these patients, 7% fulfilled echocardiographic TFC, while by the more sensitive approach, echocardiographic abnormalities were found in 64%. The according number for CMR were 34% that fulfilled CMR TFC, while 52% had CMR abnormalities (Table 2). When data from the two imaging modalities were combined, 11% fulfilled echocardiographic and/or CMR TFC, while more subtle imaging abnormalities were identified in 66% (Table 2).

Table 2
Imaging in 108 patients with no TFC-defined ECG changes.

	N	%
Age	37 ± 17	
Women	62	57
Echocardiography in patients with no ECG TFC (N = 108 of 182 patients in total)		
Any echocardiographic TFC	8	7
Any echocardiographic abnormalities	69	64
CMR in patients with no ECG TFC (N = 23 of 51 patients with available CMR)		
Any CMR TFC	8	34
Any CMR abnormalities	12	52
Imaging (echocardiography and CMR combined) in patients with no ECG TFC (N = 108 of 182 patients in total)		
Any imaging TFC	12	11
Any imaging abnormalities	71	66
Echocardiography in probands with no ECG TFC (N = 15 of 65 probands in total)		
Probands - Any echocardiographic TFC	3	20
Probands - Any echocardiographic abnormalities	9	60
Echocardiography in family members with no ECG TFC (N = 93 of 117 family members in total)		
Family members - Any echocardiographic TFC	5	5
Family members - Any echocardiographic abnormalities	60	65

Data presented as number of cases and percentage of the specified population, except for age (±SD).

We also analyzed family members without ECG TFC separately ($N = 93$, 79% of all family members): 5% fulfilled echocardiographic TFC, while 65% had individual echocardiographic abnormalities (Table 2).

3.5. Association between abnormalities, TFC and arrhythmias

In our population, arrhythmic events led to the original contact in 30% of patients (the remaining patients were evaluated as part of family screening or other symptoms), and 41% of patients fulfilled either major or minor TFC for arrhythmias (Table 1). Arrhythmic events were associated with both ECG TFC (OR 9.2, 95% CI 4.7–18.3, $P < .0001$), individual echocardiographic abnormalities (OR 2.3, 95% CI 1.1–4.6, $P < .05$), and echocardiographic TFC (OR 9.9, 95% CI 4.7–21.2, $P < .0001$) (Fig. 2). However, in a multivariate logistic regression analysis, only ECG TFC (OR 4.8, 95% CI 2.2–10.5, $P < .001$) and echocardiographic TFC (OR 4.4, 95% CI 1.9–10.4, $P < .001$) were independently associated with arrhythmic events.

4. Discussion

We found that only 4% of patients with ARVC have structural disease as defined by echocardiographic TFC without any TFC in the ECG. However, we also showed that 38% of patients had individual echocardiographic abnormalities without fulfilling ECG TFC. Importantly, only TFC were independently associated with arrhythmic events in a multivariate analysis.

4.1. A large subset of patients without ARVC-associated ECG TFC have individual echocardiographic abnormalities

Previous studies have indicated that electrophysiological abnormalities occur first in ARVC [7]. Our findings supported this idea when using imaging and ECG TFC. However, when using individual imaging abnormalities outside reference values, a large subset of patients had imaging abnormalities without concurrent ECG TFC. These findings suggest that a considerable number of patients have structurally manifest and detectable disease before they have changes in the ECG that fulfill TFC. Most likely, electrical and structural manifestations occur simultaneously, and the seemingly temporal separation is only due to the limitations of current diagnostic tools. Recent studies have reported that early signs of structural disease occur before other ARVC manifestations

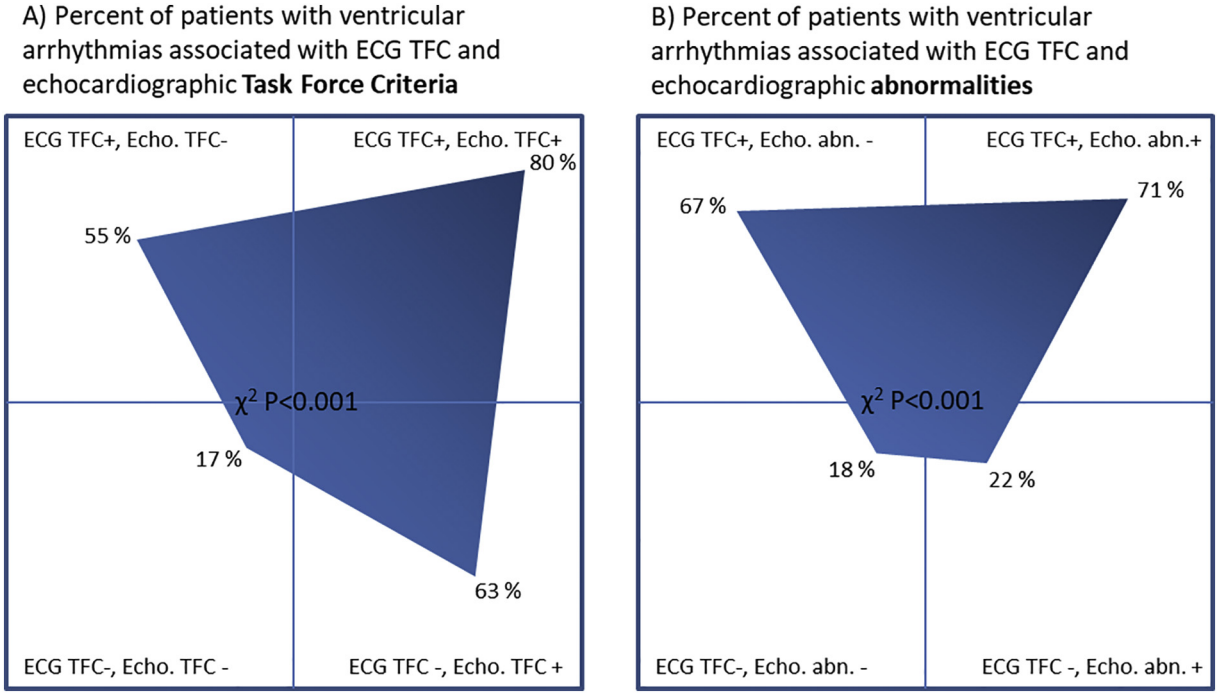

Fig. 2. Prevalence of ventricular arrhythmias according to combinations of ECG TFC and echocardiographic abnormalities or TFC. Modified radar plots of the distributions of arrhythmic events across four groups of patients with different combinations of ECG TFC and echocardiographic abnormalities or TFC. A) Percentages of patients with arrhythmic events in four groups of patients defined by coexistence of ECG TFC and echocardiographic (echo.) abnormalities (abn.). B) Percentages of patients with arrhythmic events in four groups of patients defined by coexistence of ECG TFC and echocardiographic (echo.) TFC.

in genotype positive patients when using sophisticated imaging techniques that can detect subtle changes [9].

The percentage of patients with evidence of structural disease without ECG TFC was lower when imaging TFC were used than when individual abnormalities were considered (7% versus 38%). This can be explained by the fact that imaging TFC have a higher specificity than individual abnormalities, at a cost of lower sensitivity. Fulfilled imaging TFC reflects more advanced ARVC disease, and is therefore more likely to be accompanied by ECG pathology [9,12]. Indeed, the separation between formal imaging TFC and individual abnormalities in our analysis increased the sensitivity, and thereby included more subtle structural pathology even by still using standard and well-established echocardiographic parameters. Furthermore, in patients with no ECG TFC, more patients fulfilled CMR TFC than echocardiography TFC. These results support that CMR TFC are more sensitive to detect ARVC compared to echocardiographic TFC, as reported previously [10,13,14].

4.2. Clinical implications

Although the aim of our study was to identify the proportion of patients with evidence of structural disease despite no ECG TFC, it is important to emphasize the notable sensitivity and specificity of ECG TFC, as also shown by our data. Indeed, our data support the use of several diagnostic modalities since pathology identified by echocardiography, CMR and ECG can be present independently or combined. Also, with increasing awareness of ARVC and improved availability and better resolution of cardiac imaging techniques, there may now even be a risk of over-diagnosing ARVC [15]. E.g., in competitive athletes, a substantial proportion fulfills ARVC imaging criteria with dilation of RVOT without fulfilling TFC for ARVC [16–18]. As our study shows, improved diagnostic tools to identify true ARVC are highly needed.

4.3. Limitations and future studies

The fact that echocardiographic TFC are combinations of parameters, while ECG criteria are not, affects our comparison of "individual abnormalities" to TFC. We do not claim that minor echocardiographic abnormalities are equivalent to ARVC penetrance, but we want to highlight that structural changes can appear in absence of ECG TFC. Using individual imaging abnormalities will increase sensitivity, while the combination of several abnormalities needed to fulfill imaging TFC will increase specificity of ARVC diagnosis. Several ECG and imaging parameters have been presented after the publication of the 2010 TFC, which might be considered in a future TFC re-evaluation. We did not include signal average ECG (SAECG) due to incomplete data.

We included genotype positive ARVC patients irrespective of TFC status to separate inclusion data from outcome data. Families with negative, uncertain, or unknown genetic data were therefore excluded. We cannot exclude that in the work-up of patients, information about genotype might have affected the interpretation of imaging findings, and minor echocardiographic abnormalities may have been over-interpreted. Also, a large majority (73%) of patients in our study population had *PKP2* mutations, in line with other study populations, which may have influenced our data.

The Nordic ARVC registry is a multi-center registry, based on registration of data by experts in each center. The lack of a core-lab for echocardiographic, CMR and genetic assessment is a limitation of this registry. We limited our evaluation to standard echocardiographic parameters and standard ECG as defined by the TFC to make our data relevant for the early diagnostic evaluation of patients in everyday clinical practice. Data on left ventricular characteristics and more advanced echocardiographic parameters, such as measurements of myocardial strain are therefore not included in the registry, but may enable even earlier detection of cardiac dysfunction in ARVC [9,19].

5. Conclusion

ARVC structural and ECG abnormalities may coexist or occur independently, but the prevalence strongly depend on the criteria that are used. More than one third of ARVC genotype positive patients had subtle imaging signs of disease without fulfilling ECG TFC. Although most patients will have both imaging and ECG abnormalities, disease penetrance in ARVC genotype positive patients cannot be ruled out by the absence of ECG TFC.

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ijcard.2020.05.095.

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Declaration of Competing Interests

None declared.

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